Unexplained Severe Pulmonary Hypertension in the Elderly: Report on 14 Patients

Mordechai Yigla MD[1], Mordechai R. Kramer MD FCCP[3], Daniele Bendayan MD[3], Shimon A. Reisner MD[2] and Anna Solomonov MD[1]

[1]Division of Pulmonary Medicine and [2]Echocardiography Laboratory, Department of Cardiology, Rambam Medical Center, Haifa, Israel
[3]Pulmonary Institute, Rabin Medical Center, Petah Tiqvah, Israel

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Abstract

Background: Unexplained pulmonary hypertension is assumed to occur mainly in young adults.

Objective: To describe the features of the disease in older patients and compare them to those in PHT patients of all ages.

Methods: We conducted a retrospective evaluation of the files of patients over 65 years of age in whom UPHTwas diagnosed between 1987 and 1999 at two PHT centers serving a population of 4 million. Patients were followed for survival until March 2003. Clinical variables of the study patients were compared with those in PHT patients of all ages.

Results: The study group included 14 patients, 10 females and four males, with a mean age of 70.5 ± 6.7 years. The calculated mean annual incidence of UPHT for the study population was one new case per year per million persons. Seven patients (50%) had systemic hypertension. The mean interval from onset of symptoms to diagnosis was 8.3 months. At diagnosis, 64% of patients had functional capacity of III-IV according to the New York Heart Association classification, and 43% had right heart failure. Mean systolic pulmonary artery pressure was 80 ± 21 mmHg, peripheral vascular resistance 11.7 ± 7 mmHg/L/min, cardiac index 2.16 ± 0.81, and mean right atrial pressure 10.5 ± 5.9 mmHg. Median survival time was 43 months; survival rates for 1 year, 3 years and 5 years were 92.6%, 50% and 40%, respectively. Compared to data from the U.S. National Institute of Health Registry, UPHT in older patients is more common in females, but the incidence as well as clinical, hemodynamic and survival parameters are similar to those in PHT patients at any age.

Conclusions: UPHT occurs in the elderly more frequently than previously thought, with similar features in PHT patients of all ages. The coexistence of systemic and pulmonary hypertension warrants further investigation.

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Unexplained pulmonary hypertension refers to a rare clinical syndrome characterized by increased pulmonary vascular resistance and pressure in the absence of a known cause [1,2]. The disease occurs at any age but predominantly affects young people in the third to fourth decades of life [1,2]. Untreated, pulmonary hypertension is associated with the development of right heart failure within several months to years from diagnosis [3].

Although information regarding parameters and the natural course of the disease in young patients is accumulating, less is known about the features of the disease in the elderly [4–6]. Our study examined the features of UPHT among patients over 65 years old at the time of diagnosis. Selected characteristics of clinical significance were compared with those in PHT patients of all ages.

Patients and Methods

The study included all UPHT patients over 65 years old who visited the PHT centers at Rambam Medical Center in Haifa and Rabin Medical Center in Petah Tiqva, Israel over a 12 year period between January 1987 and December 1998. The two medical centers serve a population of 4 million.

Patient evaluation

The upper limit of systolic pulmonary artery pressure in a young, healthy population using an empiric right atrial pressure of 10 mmHg has been 35 mmHg. Estimatating right atrial pressure variation of 5 mmHg, we defined PHT as a systolic PAP of 45 mmHg or more. The criteria used to establish the diagnosis of UPHT incuded systolic PAP above 45 mmHg and the absence of other conditions known to cause PHT or to be associated with a high prevalance of PHT as previously described [1,2].

Echocardiographic criteria for exclusion were global or focal systolic dysfunction, diastolic left ventricular dysfunction, valvular heart disease with moderate or greater lesion severity, or the presence of an intracardiac shunt documented by a saline solution contrast study. Diastolic dysfunction was based on well-defined criteria for the Doppler assessment of mitral inflow and pulmonary veins, and included clear restrictive, abnormal relaxation or pseudonormal filling patterns.

Disease characteristics

The data were obtained from the medical records of the corresponding medical centers, from the Bureau of Statistics or from the primary physicians. A uniform protocol was completed, including age, gender, family history of UPHT, presence of systemic diseases, and medications used (past or present), including appetite-suppressant drugs. Systemic hypertension was defined as the medical record diagnosis of hypertension plus the use of antihypertensive medication.

Symptoms leading to the diagnosis and their duration prior to

PHT = pulmonary hypertension
UPHT = unexplained pulmonary hypertension

PAP = pulmonary artery pressure

diagnosis were recorded. Disease severity as manifested by functional capacity according to the New York Heart Association classification and the presence of right heart failure on admission were documented. Other relevant factors included interpretation of X-ray and computerized tomography films of the chest, electrocardiogram, ventilation perfusion scan of the lungs, arterial blood gasses, pattern of disturbance in pulmonary function tests including single breath carbon monoxide diffusion test, and tests for autoantibodies (antinuclear, anti-DNA and antiphospholipid).

Hemodynamic studies

- *Echocardiography*. All patients underwent echo studies according to the recommendations of the American Society of Echocardiography [7]. Tricuspid regurgitation systolic jet was recorded from parasternal or apical window with the continuous wave Doppler probe. Systolic right ventricular (or pulmonary artery) pressure was calculated using the modified Bernoulli equation: PAP = 4 x (tricuspid systolic jet)2 + 10 mmHg (estimated right arterial pressure).
- *Cardiac catheterization*. Cardiac catheterization was performed as previously described [8], and right atrial pressure, pulmonary systolic, diastolic and mean pressure, pulmonary capillary wedge pressure, systemic diastolic and systolic pressure, and cardiac output were measured. Nine patients, including four suffering from arterial hypertension, underwent right heart catheterization to confirm the diagnosis of PHT. Four patients refused catheterization and one was considered too sick for the procedure.

Follow-up

The follow-up period for survival ended on 31 March 2003. The 1, 3, and 5 year survival rates from symptom onset to last follow-up visit were calculated using the Kaplan-Meier method.

Statistical analysis

Student's *t*-test and chi-square test were used for statistical analysis of the patients' clinical and hemodynamic variables. A difference of $P < 0.05$ was considered significant. Selected clinical parameters of clinical significance were compared to those of the general population as presented in the NIH registry [3] and the Israeli National Survey [9]. Selected clinical variables recorded at the time of diagnosis were correlated to subsequent mortality.

Results

Table 1 presents data on the study population, which consisted of 14 patients with UPHT who were over age 65 at the time of diagnosis. According to the Israel Bureau of Statistics, patients older than 65 years comprise 25% of the total population. Thus, the calculated mean annual incidence of UPHT for the study population is estimated as one new case per year per million persons.

The study population included 10 women and four men with a mean age of 70.5 ± 6.72 years (range 65–88 years). Six patients (43%) were older than 70 years and two were older than 80. There was no history of familial PHT or use of appetite-suppressant agents. The most frequent co-morbid condition was systemic hypertension, which was present in 50% of the patients. One patient (7%) suffered from Raynaud's phenomenon [Table 1].

Table 1. Demographic data of older patients with PPH

No.	Age/ gender	Co-morbid conditions	Symptom duration* (mos)	FC	RHF	Follow-up (mos)	Out-come
1	80/F	HTN	8	II	+	34	Alive
2	69/F	HTN	1	III	+	19	Alive
3	75/F	–	12	II	–	24	Died
4	65/F	Asthma, HTN	6	III	+	42	Alive
5**	69/F	–	6	II	–	83	Alive
6**	65/M	–	8	III	+	23	Died
7**	65/F	HTN	24	IV	+	12	Alive
8	65/M	–	12	II	–	1	Died
9**	71/F	–	1	III	–	134	Alive
10**	72/F	–	6	III	–	30	Alive
11**	71/F	HTN	3	III	–	35	Alive
12**	65/M	Raynaud's phenomenon	12	IV	+	24	Alive
13**	67/M	HTN, obesity	6	II	–	27	Alive
14**	88/F	HTN	12	II	–	12	Alive

* Duration of symptoms before the diagnosis of pulmonary hypertension.
** Patients underwent right side cardiac catheterization.
FC = functional capacity according to NYHA criteria at diagnosis; RHF = findings of right heart failure at diagnosis; HTN = systemic hypertension.

Presenting symptoms

Dyspnea, present in all the patients, and chest pain, present in five (36%), were the leading symptoms. Six patients (42%) had pedal edema, and two (14%) had fatigue and cyanosis as well. Mean time interval from onset of symptoms to diagnosis was 8.3 ± 5.93 months (range 1–24 months). NYHA class at diagnosis was II for 5 patients (36%), III for 7 (50%), and IV for 2 (14%). Six patients (43%) presented with right heart failure [Table 1].

Laboratory tests

Chest radiography showed an enlarged heart silhouette in 10 patients (71.4%), enlarged pulmonary arteries in 12 (85.7%), and decreased vascular marking in 7 (50%). ECG demonstrated sinus rhythm in all patients, and 10 patients (71.4%) had right axis deviation and right ventricular hypertrophy. Autoantibody tests were positive to cardiolipin in one patient. Lung scan showed non-homogeneous perfusion, indicating a low probability for pulmonary embolism in all cases. Pulmonary function tests showed normal lung volume and flow rate in 11 patients (79%), 2 had mild airflow obstruction (forced expiratory volume in 1 second of 73%, 74%) and one had mild restriction (due to pleural effusion). Nine patients (64%) had reduced diffusion capacity (35–66% of predicted values). Arterial blood gases sampled while breathing room air showed partial pressure for oxygen of 68 ± 12 mmHg (range 54–89) and for carbon dioxide 36 ± 7 mmHg (range 28–47).

NIH = National Institutes of Health

NYHA = New York Heart Association

Table 2. Arterial blood gasses and hemodynamics in nine elderly patients with UPHT

	Mean ± SD (range)
Arterial blood gases (on room air)	
Oxygen saturation (%)	93 ± 3 (88–97)
CO_2 partial pressure (mmHg)	36 ± 7 (28–47)
O_2 partial presure (mmHg)	68 ± 12 (54–89)
Catheterization data	
Systolic pulmonary artery pressure (mmHg)	80 ± 21 (46–119)
Right atrial pressure (mmHg)	10.5 ± 5.9 (4–20)
Cardiac index (L/min/m)	2.16 ± 0.81 (1.3–3.6)
Peripheral vascular resistance (mmHg/L/min)	11.7 ± 7 (4.1–15)
Systemic vascular resistance (mmHg/L/min)	28.7 ± 16.8 (11.7–55.9)

Hemodynamic findings

Echocardiography demonstrated enlarged right atrium and ventricle, paradoxical septal motion and tricuspid regurgitation in all patients and an estimated mean systolic PAP of 80 ± 21 mmHg (range 46–119). The results of right heart catheterization studies (available for nine patients, four of them with arterial hypertension) are presented in Table 2. Pulmonary vascular resistance was 11.7 ± 7 mmHg/L/min (range 4.1–15), with a mean right atrial pressure of 10.5 ± 5.9 mmHg (range 4–20) and a cardiac index of 2.16 ± 0.81 L/min/m (range 1.3–3.6). All patients had normal pulmonary capillary wedge pressure without left-to-right shunt.

Therapy

All patients received oral vasodilators, slow-release calcium channel-blocking agents (Osmo-Adalat®, 30–240 mg/day, Pharma Clal, Israel) and anticoagulants (warfarin), with INR values 2–3. Two patients received, in addition, chronic continuous intravenous infusion of prostoglandin (Flolan®, Glaxo-Wellcome, UK) through a catheter placed in a central vein via a pump, and one patient received inhalation of ilomedine (Iloprost®, Schering, Germany).

Follow-up and survival

Length of follow-up was less than one year for one patient who died, 1–3 years for 10 patients and more than 3 years for the remaining 3 patients. By the end of March 2003, 11 patients were alive. The mean survival rate was 43 months (range 12–134). The 1, 3, and 5 year survival rates were 71.4%, 50% and 40%, respectively. For the three patients who died the cause of death was right heart failure. There was no correlation between the clinical and hemodynamic variables observed at presentation and survival.

Table 3 presents clinical data on older patients enrolled in this study as compared to PHT patients of all ages (NIH registry [3] and the Israeli Survey [9]). Compared with non-selected UPHT patients, this group of older UPHT patients had a higher female:male ratio. Older patients presented with similar symptoms but had a non-significant shorter time interval from symptom onset to diagnosis (8.3 vs. 24 months). Incidence and clinical variables in older patients regarding disease severity at presentation and survival parameters did not differ significantly from those of non-selected UPHT patients [3].

Table 3. Data on older patients with PPH compared to PHT patients of all ages

	Older patients (>65 yrs) (n=14)	NIH PPH Registry (n=187)	Israel National Survey (n=44)
Age (yrs)			
Mean ± SD	70.5 ± 6.7	36.4 ± 15	42.8 ± 13
Range	65–88	1–81	16–63
F/M ratio	2.5/1	1.7/1	3.4/1
Incidence	1.0x1x106/year	1–2x106/year	1.4x106/year
Common symptom	Dyspnea	Dyspnea	Dyspnea
Mean duration of symptoms before diagnosis (yrs)	8/12	2	2.9
Functional capacity (NYHA)			
1–2	36%	29%	48%
3–4	64%	71%	52%
Systolic PAP (mmHg)			
Mean ± SD	80 ± 21	60 ± 18	61 ± 16
Range	46–119	28–127	37–95
Cardiac index (L/min/m)			
Mean ± SD	2.16 ± 0.81	2.27 ± 0.9	2.48 ± 0.8
Range	1.3–3.6	0.8–7.9	0.9–4.6
Survival			
Median (yrs)	2.3	2.8	4.0
1 year	92.6%	68%	82%
3 years	50%	48%	57%
5 years	40%	34%	43%

Discussion

Primary or unexplained PHT has been reported mostly in the younger population group. The disease has also been reported in older populations but to a much lesser extent. For example, only 9% of the patients included in the National Registry for PPH [3] were in the seventh decade of life [3]. In a literature review, we found only three reports of UPHT in 18 older patients [4–6]. Phipps et al. [4] described two patients with severe UPHT diagnosed in the sixth and seventh decades of life after prolonged symptomatic periods of 2 and 5 years, who died 2 years after diagnosis. We reported right heart failure at presentation among six of eight UPHT patients aged 51–82 years, with accelerated course and median survival of 6 months [5]. Braman and collaborators [6] reported eight UPHT patients over 65 years old with a high rate of initial false diagnosis, although their presenting symptoms were typical, causing a diagnostic delay.

The current study examined, for the first time, the parameters of UPHT among elderly patients and found an unexpectedly high incidence, which is greater than previously considered [1,2] and similar to incidence rates in the general population (1 vs. 1 to 2 new cases per year per million citizens, respectively).

After many years of clinical and experimental studies that have increased our understanding of the pathogenesis of this mysterious disease [10], it is still not clear why the disease is more common in young people. As the vulnerability of younger subjects has yet to be proven, similar incidence rates of UPHT in young and older population groups appear to be reasonable from an epidemiologic point of view.

UPHT is associated with exertional dyspnea and decreased

physical fitness, not uncommon complaints among elderly subjects. Consequently, the possibilty of a selection bias favoring echocardiographic studies of younger patients with unexplained dyspnea has been raised. The relatively higher proportion of elderly patients among newly diagnosed UPHT cases in our facilities might be explained by the routine use of Doppler echocardiography to screen patients at any age with typical symptoms, such as unexplained dyspnea and syncope [11]. This policy may lead to the diagnosis of older patients who otherwise might not be diagnosed.

Since the presenting symptoms of UPHT are not specific and not uncommon in the elderly, diagnostic delays or even missed diagnoses are anticipated [12]. A trend not to perform right cardiac catheterization – the most accurate procedure for the diagnosis of PHT – in older patients because of its side effects may contribute further to the under-diagnosis of the disease [8]. In our hospitals, older patients with UPHT presented with the typical symptoms, had a short mean time interval from onset of symptoms to diagnosis (8.3 months), and had similar clinical, hemodynamic and survival parameters as compared to non-selected UPHT patients [3,9].

The current study shows an unexpectedly high incidence (50%) of systemic and pulmonary hypertension in patients above age 65. One possible explanation is that the proportion of arterial hypertension among UPHT patients is similar to the proportion of hypertension in the general population in this age group (estimated as 50%). Another possibility is that left ventricular diastolic dysfunction could lead to PHT. Although we excluded all patients with clear Doppler evidence of left ventricular diastolic dysfunction, this does not exclude the possibility of subtle diastolic dysfunction as the mechanism of PHT. The catheterization studies of nine patients, including four with arterial hypertension, showed normal pulmonary capillary wedge pressure, arguing against left ventricular diastolic dysfunction as the cause for this PHT.

In a recent study, Finkelhor et al. [13] investigated the validity of the association between systemic hypertension and UPHT diagnosed by Doppler echocardiography. They noted that UPHT occurred mostly in the elderly (mean age 70 years), was associated with high frequency (98%) of systemic hypertension, and that hypertensive patients with UPHT have higher systolic systemic arterial pressures than matched controls without UPHT. The authors suggested that a possible mechanism for the association of arterial and pulmonary hypertension could be an exaggerated endothelial response to vasoconstrictor stimuli, both in the systemic and pulmonary vasculature of the patients.

The survival of patients suffering from long-standing PHT of any cause depends on the adaptation of the right ventricle to the chronic overloaded pressure state [3,11]. Long-standing PHT is expected to affect prognosis. Contrary to previous reports, elderly UPHT patients in our institutions were diagnosed relatively early, probably due to the institutional experience in this area. This might explain similar survival rates among older patients even in the presence of coexisting medical problems, including arterial hypertension.

Conclusions

UPHT does occur in the elderly, perhaps more frequently than previously thought, and is characterized by a similar incidence and clinical, hemodynamic and survival parameters as in PHT patients of all ages. A high prevalence of arterial and pulmonary hypertension in elderly patients warrants further investigation.

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Correspondence: Dr. M. Yigla, Division of Pulmonary Medicine, Rambam Medical Center, Haifa 31096, Israel.
Phone: (972-4) 854-2650
Fax: (972-4) 854-2031
email: m_yigla@rambam.health.gov.il

Iron rusts from disuse, stagnant water loses its purity and in cold weather becomes frozen; even so does inaction sap the vigor of the mind

Leonardo da Vinci (1452-1519), Italian artistic and scientific genius of the Renaissance